Coumarin Therapy

Prothrombin Activity After Termination of Treatment

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• **Twelve patients receiving coumarin type hypoprothrombinemic agents were studied before, during and after termination of therapy, the prothrombin proconvertin method having been used to assay the prothrombin activity complex.**

In no instance was post treatment "rebound" demonstrated.

Prothrombin activity levels returned to pretreatment values only after ten days following termination of coumarin or Dicumarol administration.

If a reactivation of thrombotic tendency occurs following discontinuance of anticoagulant therapy, it would not appear to be related to a "rebound" of prothrombin activity above that which is "normal" for the individual patient.

Patients tend to return to the same level of prothrombin activity present before initiation of coumarin therapy.

THE FEASIBILITY and practicality of anticoagulant therapy are well established. The results, as judged by decreased incidence of recurrent myocardial infarction, have encouraged widespread use of such agents as Dicumarol® and coumarin.

Although the use of anticoagulants can safely be continued over long periods, it may eventually be desirable in some cases to terminate use of the drugs. Occasionally an apparent reactivation of thrombotic tendency follows discontinuation of anticoagulant therapy. This is at times a drastic occurrence, seriously threatening the life of the patient. It is possible that such events are fortuitous extensions of chronic vascular change; on the other hand, the second thrombotic episode might be related to a hypercoagulable state.

There is general agreement that the use of coumarin derivatives is associated with a decrease in plasma levels of prothrombin, proconvertin, plasma thromboplastin component and Stuart factor.

It has been suggested that the recurrence of a hypercoagulable state might be related to a "rebound" of these factors whose production was inhibited during the period of treatment. If a rebound phenomenon were the anticipated result of abrupt termination of therapy, one might reasonably propose to alter the therapeutic regimen to allow for a tapering period.

A number of workers have been intrigued by the occurrence of thrombosis following cessation of anticoagulant therapy and have undertaken studies in an attempt to determine if demonstrable changes occurred in coagulation systems on the abrupt discontinuance of coumarin derivatives.

Dixon and Vander Veer,[1] who did such a study, said: "It has been our impression that the reactivation of the original pathologic process and various thromboembolic complications may follow the abrupt cessation of anticoagulants. These occurrences have often been dramatic and catastrophic." In their study of 20 case histories, they were unable to decide if the thrombotic recurrences were due to the mode of withdrawal from the drug, or to the mere cessation of anticoagulant therapy.

Sise,[2] in a study of 239 patients on long term therapy, concluded that stopping anticoagulants for brief periods for tooth extractions or other surgical procedures involves no great risk. On the other hand, if bleeding occurs, necessitating sudden withdrawal of anticoagulants and administration of vitamin K_1, one may anticipate complications in the form of myocardial infarctions, sudden death or stroke in approximately 50 per cent of patients.

Various hypotheses have been offered to explain these observations; Dixon and Vander Veer suggested two possible causes: (1) "Rebound hypercoagulation, and (2) the possible effects of anticoagulants (and their discontinuance) on a disordered coronary blood flow.

MATERIAL AND METHODS

The present study was undertaken to see if a rebound period of hypercoagulation could be demonstrated. Plasma prothrombin activity was measured in patients during anticoagulant therapy and more particularly during the period immediately following termination of this therapy.

The study included patients scheduled to receive coumarin therapy for various thrombotic states on

Submitted March 20, 1963.
Supported by a grant from Orange County Heart Association.

TABLE 1.—*Clinical Indications for Anticoagulants and Secondary Diagnosis of the Patients Under Consideration*

Patients	Primary Disease	Age	Duration of Treatment* Days	Reversal Period† Days
1	Myocardial infarction	50	37	10
2	Myocardial infarction	71	14	7
3	Myocardial infarction	82	15	12
4	Myocardial infarction	42	19	14
5	Myocardial infarction	45	43	7
6	Myocardial infarction	73	29	21
7	Myocardial infarction	75	31	11
8	Carotid artery insufficiency	65	89	10
9	Myocardial infarction	78	15	9
10	Myocardial infarction	66	20	8
11	Myocardial infarction	63	58	7
12	Rheumatic heart disease, fibrillation, emboli	52	67	10

*Days prothrombin activity under 50 per cent.

†Days from termination of treatment to return to stabilization of prothrombin activity.

the medical service of a large general hospital. The age span of these patients was from 42 to 82 years. The patients under study received either coumarin or Dicumarol. The period of therapy ranged from 12 to 89 days with prothrombin values in therapeutic range. Patients were observed for from six to twenty-two months after cessation of therapy.

Laboratory studies included an estimation of prothrombin activity as determined by the Ware-Stragnell[3] modification of the prothrombin proconvertin system. This test was chosen because it utilizes a dilute plasma system, and accordingly is sensitive to higher values of the prothrombin activity complex. Prothrombin activity of the patients under study was determined before initiation of treatment and during treatment. Following conclusion of treatment, determinations were continued until prothrombin activity levels had stabilized for one week. (A number of patients had to be removed from the study group because there was inadequate follow-up preceding discharge from the hospital.) Adequate clinical and laboratory observation was available on 12 patients.

RESULTS

Table 1 summarizes the variety of indications for anticoagulant therapy in the patients considered in this study. For purposes of this table, duration of therapy is defined as that period of time during which prothrombin activity was assigned a value of 100 per cent. Thus a total of 12 patients varying in age from 42 to 82 years received either Dicumarol or coumarin (Warfarin) for a period ranging from 18 to 89 days. Following termination of therapy the prothrombin activity stabilized in from 7 to 21 days at a level comparable to pretreatment activity.

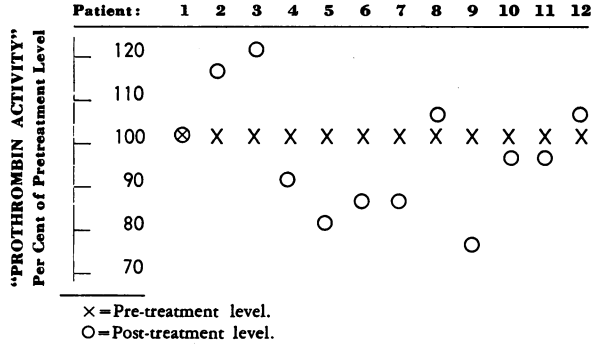

Chart 1.—Post-therapy levels of prothrombin activity related to pretreatment level for each patient.

This point is further demonstrated in Chart 1 where post-therapy levels of prothrombin activity are related to the individual's pretreatment prothrombin activty taken as 100 per cent. On this basis the patient's post-therapy level of activity is properly compared with his own pretreatment level rather than with an arbitrary standard. Of some interest is the observation that pretreatment levels were not achieved for an average of ten days after therapy was discontinued. In this small series the time required from abrupt termination of anticoagulant therapy until pretreatment prothrombin activity was achieved, ranged from 7 to 21 days. There was no recurrence of thrombosis in less than six months.

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